

Transmission of Human Immunodeficiency Virus from Parents to Only One Dizygotic Twin

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The acquired immunodeficiency syndrome-related complex was identified in a mother and one of her nonidentical twins. Generalized lymphadenopathy was first noted in the infant at age 17 months, and that of the mother was incidentally discovered 6 months later. The father, who had had homosexual contacts before the conception of the twins, appeared to be in good health. No one in the family had constitutional symptoms or showed signs of opportunistic infection. Both parents and the patient had hypergammaglobulinemia, low T-helper-to-suppressor-cell ratio, and positive serum antibody to human immunodeficiency virus. Attempts to isolate the virus from all family members were unsuccessful. The twin brother was in good health with a normal immunologic profile and negative antibody to human immunodeficiency virus.

Acquired immunodeficiency syndrome (AIDS) is a transmissible disease of the immune system, thought to be caused by a newly recognized human retrovirus, human immunodeficiency virus (HIV), formerly known as human T-cell lymphotropic virus type III, lymphadenopathy-associated virus, or AIDS-related virus (5, 17-19). HIV appears to be transmitted by intimate contact, by transfusion of contaminated blood or blood by-products, or from infected mothers to children. High-risk groups for AIDS include homosexuals, heterosexual partners of HIV-infected persons, intravenous drug users, hemophiliacs, recipients of blood products from an infected donor, and children of high-risk parents (1, 19). As of January 1987, 422 patients under 13 years of age with AIDS have been reported to the Centers for Disease Control. The majority, 337, are the offspring of mothers in a high-risk group, and 50 had a history of transfusions with blood or blood components before the onset of illness. Possible transmission of AIDS from mother to infant in utero has been reported as early as in a 20-week-old fetus and postnatally (1, 3, 6, 8, 11, 16, 20, 22).

We describe a family in which HIV infection was found in the parents and one twin and lymphadenopathy syndrome was found in the mother and the child, suggesting transmission of HIV from the mother to only one twin.

Case reports. (i) Patient. The patient was born at 39 weeks of gestation by normal vaginal delivery, the first born of nonidentical twins, and weighed 4 lb, 15 oz (ca. 2,240 g). He was immunized with diphtheria-pertussis-tetanus (DPT) and oral polio vaccines at 2, 4, and 6 months without deleterious effects. The lymphadenopathy, which was first noted at 17 months, started in the postauricular area and spread to the cervical, axillary, and inguinal areas during the following 4 months. At 21 months, the lymph nodes were nontender, matted together, 3 to 5 cm in size, and fixed to the underlying soft tissue, and the patient was sent to the oncology clinic. Hepatosplenomegaly never developed, and the health of the patient had been good without any history of fever or weight loss. Tuberculin skin tests were negative at 12 and 18 months of age. Serial complete peripheral blood counts and a chest X ray were normal. Serologic tests for syphilis, toxoplasma,

rubella, herpesvirus, and cytomegalovirus were negative. Bone marrow aspiration showed a normal cellularity with a normal maturation pattern. Cultures of axillary lymph node tissue were negative for bacteria, viruses, fungi, and mycobacteria. Lymph node biopsy showed marked reactive follicular hyperplasia with loss of demarcation of germinal centers and sinusoidal infiltration of polymorphonuclear cells and "monocytoid" cells. During the 1-year follow-up, the patient continued to grow along the 10th percentile and reached the developmental milestones a couple of months behind his twin brother. He has not shown any evidence of opportunistic infections.

(ii) Mother. The mother is a 23-year-old female who had open-heart surgery for the repair of an atrial septal defect 6 years ago. One year later, she developed hyperthyroidism and was treated with propylthiouracil for 6 months. She stated that her only sexual contact for the last 4 years had been the father of the twins and that she had a 1-year history of recurrent genital herpes. The mother did not have a thorough physical exam until 6 months after the onset of the patient's lymphadenopathy, when she developed acute diarrhea and was seen in our emergency room. Generalized lymphadenopathy in the cervical, supraclavicular, axillary, and inguinal areas was discovered during physical examination. The lymph nodes were firm, nontender, matted together, and 2 to 4 cm in size. The thyroid gland was diffusely enlarged without palpable nodules. A grade II ejection systolic murmur was audible at the base of the heart. The rest of her physical examination was unremarkable. Culture of her stool grew *Campylobacter jejuni* but was negative for viruses, fungi, and parasites. The diarrhea resolved without specific treatment. Further evaluation for the generalized lymphadenopathy showed mild normochromic, normocytic anemia (hemoglobin, 10.4 g/dl), normal absolute neutrophil and lymphocyte counts, and panhypergammaglobulinemia. Serology for cytomegalovirus and toxoplasma was negative, as was the Venereal Disease Research Laboratory test. Her thyroid function and chest X ray were within normal limits. Axillary lymph node biopsy showed marked follicular hypertrophy with areas of germinal center lysis. Cultures of lymph node tissues were negative. The patient failed to return to the clinic for follow-up but reported over the telephone that she had been feeling well without any consti-

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TABLE 1. Humoral immune functions

Subject	Immunoglobulins (mg/dl)			Isohemagglutinin		Anti-diphtheria toxin antibody (ng of toxin nitrogen bound/ml) ^a	Anti-HIV antibody ^b
	G	A	M	Anti-A	Anti-B		
Patient	2,710	150	400	NA ^c	1:64	51 ^d	+
Brother	940	36	130	ND ^e		4,807 ^d	—
Mother	4,000	132	184	1:16	1:32	15 ^f	+
Father	3,520	198	180	NA	1:4	140 ^f	+

^a Normals: more than 100 ng of toxin N bound per ml after three immunizations.

^b Determined by Western blot strip radioimmunoassay.

^c NA, Not applicable (subjects were blood group A).

^d Subjects were immunized with DPT at the same time, at 2, 4, and 6 months of age.

^e ND, Not done.

^f Subjects were immunized with DPT more than 10 years ago.

tutional symptoms suggestive of opportunistic infection or recurrence of hyperthyroidism.

(iii) **Father.** The father, a 23-year-old male, had homosexual contact with multiple partners for about a year before the conception of the twins. His only prior illness occurred 5 years ago, when he was hospitalized elsewhere for an acute massive lower gastrointestinal hemorrhage. He required more than eight units of blood (unscreened for HIV), but the source of bleeding was not identified. He is in good health without lymphadenopathy.

(iv) **Brother.** The twin brother is in good health. His birth weight was 5 lb, 14 oz (ca. 2,665 g), and both his height and weight are at the 75th percentile for age. He has always been heavier and reached age-appropriate developmental milestones a couple of months earlier than the patient.

Laboratory findings. (i) **Humoral immune functions.** The results of the humoral studies are shown in Table 1. The patient and both parents had marked polyclonal hypergammaglobulinemia (determined by radial immunodiffusion), which was again noted 3 months later. The patient and parents had measurable serum isohemagglutinins, although the isohemagglutinin titer of the father was extremely low. Serum diphtheria antitoxin concentrations, measured by radioimmunoassay, were low in the mother and patient. Despite the twins having received DPT simultaneously during well-baby-clinic visits at 2, 4, and 6 months of age, the serum antitoxin concentration of the twin brother was 4,807 ng of toxin N bound per ml of serum, while the serum of the patient bound only 51 ng of toxin N per ml of serum. The patient's anti-Epstein-Barr virus-viral capsid antigen titer was 1:640 3 months after the onset of the generalized lymphadenopathy. Seven months later, anti-Epstein-Barr virus nuclear antigen antibody appeared (1:80), which is a characteristic pattern of past Epstein-Barr virus infection. Large amounts of circulating immune complexes were detected by the solid-phase Clq-binding assay in the patient's serum but were undetectable by Raji cell radioimmunoassay. Serum antibody against HIV was positive by enzyme-linked immunosorbent assay and Western blot assay in the parents and patient. In the brother, anti-HIV antibody was equivocal by enzyme-linked immunosorbent assay (not a commercial assay) but negative by Western blot assay. We were unable to culture HIV from peripheral blood mononuclear cells of all family members during a single attempt.

(ii) **Cellular immune functions.** All family members had normal absolute lymphocyte counts on several occasions (Table 2). Circulating T-cell (sheep erythrocyte rosette-forming cells) numbers were low only in the patient (35%).

When his peripheral blood mononuclear cells were stained with monoclonal antibody Leu 1 (pan-T cell marker; Becton Dickinson and Co., Mountain View, Calif.), 30% were brightly stained and 28% were weakly stained. The parents and the patient showed decreased circulating T-helper lymphocytes (Leu 3a-stained cells). Both the father and the patient had slightly increased T-suppressor lymphocytes (Leu 2a-stained cells). The T-helper-to-suppressor-cell ratio was depressed in the patient, mother, and father. The lymphocyte proliferative responses of the parents and patient to mitogens and alloantigens were all within normal limits. The mother and both twins showed positive delayed-type skin sensitivity to tetanus toxoid.

Discussion. Although virus was not isolated from the family, the presence of serum antibody to HIV and the history of the parents strongly suggest HIV infection and diagnosis of lymphadenopathy syndrome in the mother and patient (1, 12, 14, 15). The brother did not have detectable serum antibodies to HIV or detectable virus in circulating blood mononuclear cells, but these findings do not necessarily rule out seronegative infection (12, 14, 15).

Although postnatal transmission of HIV from parents to one twin is theoretically possible, a recent epidemiological study suggests that the risk of horizontal transmission among nonsexual household contacts is minimal (4). HIV can be transmitted through breast milk postnatally (22), but the twins were never breast-fed. The most likely mode of transmission of the virus from the mother to the patient was transplacentally or perinatally. Since transplacental transmission of the virus during an early gestational stage with possible late expression of the disease seems to occur in pediatric cases of AIDS (3), this appears to be the most plausible explanation. In utero transmission of AIDS has been well described in several reports (3, 8, 11, 20) and as early as in a 20-week fetus (6). The precise mechanism of transmission of HIV is not known. It is conceivable that the virus gains entry to the fetus transplacentally, by maternal-fetal transfusion, via ascending infection from the maternal genital tract, or via exposure of superficial abrasion or mucosal membrane by infected maternal blood in the birth canal during labor. Since the twins in this report are nonidentical, differing degrees of exposure to maternal blood or cervical secretion could have occurred. Higher rates of colonization by mycoplasma in the first born of twins of mothers carrying genital mycoplasma have been reported (7). Such occurrences were thought to be the result of an ascending infection from the maternal genital tract. Intra-uterine viral infections affecting one twin but not the other were previously documented (2). A remote but interesting possibility is different susceptibilities of the twins to HIV infection and expression of disease due to inherent resistance or the lack of a host factor or factors which favor the HIV infection. The importance of host factors in HIV infection has been suggested by the relatively rare occurrence of AIDS after transfusion and the higher incidence of transfusion-associated AIDS in premature infants after a relatively short incubation period (11, 13). In a recent report of a 3-year prospective study of healthy seropositive homosexual men, Weber et al. reported that an episode of sexually transmitted disease was the most important prognostic factor, suggesting the possibility that a host cofactor is important in determining progression of the disease after HIV infection (10, 21).

A case of maternally transmitted HIV infection to only one of nonidentical twins has been reported (20). Recently, Menez-Bautista et al. reported monozygotic twins discor-

TABLE 2. Cellular immune functions

Subject	Absolute lymphocyte count/ml	T cells (% erythrocyte rosettes)	T helper cells (% Leu 3a +)	T suppressor cells (% Leu 2a +)	T helper/suppressor ratio	Lymphocyte mitogen response (cpm [10^3]) ^a				Mixed leukocyte culture (cpm [10^3]) (SI) ^b	Skin test result	
						PHA	ConA	PWM	Back-ground		<i>Candida</i>	Tetanus toxoid
Patient	3,700	35	11	33	0.3	199	79	88	2	24 (10)	—	+
Brother	2,720	58	49	19	2.6	136	52	42	0.6	52 (9)	—	+
Mother	1,910	78	12	22	0.5	110	42	32	0.7	62 (14)	—	+
Father	3,470	72	29	40	0.7	199	121	159	0.8	76 (21)	ND ^c	ND
Normal control ^d		61–83	41–49	15–27	1.2–3.0	100–324	39–123	31–235	0.1–1.8	(25)		

^a Cultured for 3 days. PHA, Phytohemagglutinin; ConA, concanavalin A; PWM, pokeweed mitogen.

^b Cultured for 5 days. The stimulation index (SI) is shown in parentheses.

^c ND, Not done.

^d Normal ranges at our laboratory.

dant for AIDS (9). The patient received a partial-exchange transfusion shortly after birth. Although the donor of the plasma used in the exchange transfusion was seronegative, there remains the remote possibility that the donor was a seronegative viremic individual (12, 14).

To date, none of the family members has complained of constitutional symptoms or shown signs of infection with opportunistic agents, but both the mother and the patient showed slow progression of their lymphadenopathy during 1 year of follow-up. Since the incubation period of AIDS is fairly long, and only about a fraction of the patients with AIDS-related complex have progressed to AIDS (17–19, 21), it remains to be seen whether the members of this family will eventually develop overt AIDS.

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LITERATURE CITED

1. Ammann, A. J. 1985. The acquired immunodeficiency syndrome in infants and children. *Ann. Intern. Med.* **103**:734–737.
2. Cooper, L. Z. 1985. The history and medical consequences of rubella. *Rev. Infect. Dis.* **7**(Suppl.):2–15.
3. Cowan, M. J., D. Hellmann, D. Chudwin, D. W. Wara, R. S. Chang, and A. J. Ammann. 1984. Maternal transmission of acquired immune deficiency syndrome. *Pediatrics* **73**:382–386.
4. Friedland, G. H., B. R. Saltzman, M. F. Rogers, P. A. Kahl, M. L. Lesser, M. M. Mayers, and R. S. Klein. 1986. Lack of transmission of HTLV-III/LAV infection to household contacts of patients with AIDS or AIDS-related complex with oral candidiasis. *N. Engl. J. Med.* **314**:344–349.
5. Gallo, R. C., S. Z. Salahuddin, M. Popovic, G. M. Shearer, M. Kaplan, B. F. Haynes, T. J. Palker, R. Redfield, J. Oleske, B. Safai, G. White, P. Foster, and P. D. Markham. 1984. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* **224**:500–503.
6. Jovaisas, E., M. A. Koch, A. Schafer, M. Stauber, and B. Lowenthal. 1985. LAV/HTLV-III in 20 week fetus. *Lancet* **ii**:1129.
7. Klein, J. O., D. Buckland, and M. Finland. 1969. Colonization of newborn infants by mycoplasmas. *N. Engl. J. Med.* **280**:1025–1030.
8. Lapointe, N., J. Michaud, D. Pekovic, J. P. Chausseau, and J. M. Dupuy. 1985. Transplacental transmission of HTLV-III virus. *N. Engl. J. Med.* **312**:1325–1326.
9. Menez-Bautista, R., S. Fikrig, S. Pahwa, M. G. Sarangadharan, and R. L. Stoneburner. 1986. Monozygotic twins discordant for the acquired immunodeficiency syndrome. *Am. J. Dis. Child.* **140**:678–679.
10. Montagnier, L. 1985. Lymphadenopathy-associated virus: molecular biology to pathogenicity. *Ann. Intern. Med.* **103**:689–693.
11. Oleske, J., A. Minnenor, R. Cooper, Jr., K. Thomas, A. Cruz, H. Ahdieh, I. Guerrero, V. V. Joshi, and F. Desposito. 1983. Immunodeficiency syndrome in children. *J. Am. Med. Assoc.* **249**:2345–2349.
12. Pahwa, S., M. Kaplan, S. Fikrig, R. Pahwa, M. G. Sarangadharan, M. Popovic, and R. C. Gallo. 1986. Spectrum of human T-cell lymphotropic virus type III infection in children. *J. Am. Med. Assoc.* **255**:2299–2305.
13. Peterman, T. A., H. W. Jaffe, P. M. Feorino, J. P. Getchell, D. T. Warfield, H. W. Haverkos, R. L. Stoneburner, and J. W. Curran. 1985. Transfusion-associated acquired immunodeficiency syndrome in the United States. *J. Am. Med. Assoc.* **254**:2913–2917.
14. Salahuddin, S. Z., J. E. Groopman, P. D. Markham, M. G. Sarangadharan, R. R. Redfield, M. F. McLane, M. Essex, A. Sliski, and R. C. Gallo. 1984. HTLV-III in symptom-free seronegative persons. *Lancet* **ii**:1418–1420.
15. Sarngadharan, M. G., M. Popovic, L. Bruch, J. Schupbach, and R. C. Gallo. 1984. Antibodies reactive with human T-lymphotropic virus; HTLV-III in the serum of patients with AIDS. *Science* **224**:506–508.
16. Scott, G. B., B. E. Buck, J. G. Leterman, F. L. Bloom, and W. P. Parks. 1984. Acquired immunodeficiency syndrome in infants. *N. Engl. J. Med.* **310**:76–81.
17. Selwyn, P. 1986. AIDS: what is now known, I. *Hosp. Pract.* **21**:78–82.
18. Selwyn, P. 1986. AIDS: what is now known, II. *Hosp. Pract.* **21**:127–164.
19. Shannon, K. M., and A. J. Ammann. 1985. Acquired immune deficiency syndrome in childhood. *J. Pediatr.* **106**:332–342.
20. Vilmer, E., A. Fischer, C. Griscelli, F. Barre-Sinoussi, V. Vie, J. C. Chermann, L. Montagnier, C. Rouzioux, and F. Bran-Vezinet. 1984. Possible transmission of a human lymphotropic retrovirus (LAV) from mother to infant with AIDS. *Lancet* **ii**:229–230.
21. Weber, J. N., J. Wadsworth, L. A. Rogers, O. Moshtael, K. Scott, T. McManus, E. Berrie, D. J. Jeffries, J. R. W. Harris, and A. J. Pinching. 1986. Three-year prospective study of HTLV-III/LAV infection in homosexual men. *Lancet* **i**:1179–1182.
22. Ziegler, J. B., D. A. Cooper, R. O. Johnson, and J. Gold. 1985. Post-natal transmission of AIDS-associated retrovirus from mother to infant. *Lancet* **i**:896–897.